37
Appendiceal Neoplasms

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Abbreviations

AJCC	American Joint Commission on Cancer
DPAM	Disseminated peritoneal adenomucinosis
ENETS	European Neuroendocrine Tumor Society
HIPEC	Hyperthermic (or heated) intraperitoneal chemotherapy
LAMN	Low grade appendiceal mucinous neoplasms
PCI	Peritoneal carcinomatosis index
PMAC	Peritoneal mucinous adenocarcinomatosis
PMCA	Peritoneal mucinous carcinomatosis
PMP	Pseudomyxoma peritonei

Key Concepts

- Although appendectomy for appendicitis is the most common emergency operation performed by general surgeons, primary neoplasms of the vermiform appendix are rare, and each individual general surgeon will have limited personal experience in the management of such lesions.
- Most primary neoplasms of the appendix are not associated with specific signs or symptoms and are incidentally diagnosed after pathological analysis of the appendectomy specimen, or detected incidentally on imaging such as computed tomography (CT) done for other indications.
- Primary neoplasms of the appendix can generally be divided into epithelial, non-epithelial, and mixed lesions. Epithelial lesions include adenoma and adenocarcinoma. Non-epithelial tumors include neuroendocrine tumors (carcinoids), lymphoma, leiomyoma, leiomyosarcoma, and other even rarer rarities. Goblet cell carcinoids are mixed lesions with features of carcinoid as well as mucinous adenocarcinoma.
- Epithelial tumors, and specifically mucinous adenocarcinomas, are the most common primary appendiceal neoplasms.
- Pseudomyxoma peritonei is the result of a perforation and peritoneal dissemination of a mucin-producing epithelial neoplasm, most commonly originating from the appendix or the ovaries. In select patients, cytoreductive surgery with HIPEC should be considered.
- A mucocele is a morphologic cystic manifestation of an epithelial appendiceal neoplasm. Perforation leads to pseudomyxoma peritonei. Therefore, intact removal en-bloc is of utmost importance.
- Appendiceal carcinoids are rarely associated with carcinoid syndrome or multicentricity.
- The newest tumor staging guidelines distinguish appendiceal tumors from colon cancer, and separate between epithelial and non-epithelial lesions.
- The extent of surgical resection depends on the cell type, preoperative staging, the ability to achieve negative resection margins, and the probability of nodal disease.
- Surgery is the primary treatment for localized disease, whereas its role in metastatic disease needs to be individually analyzed and weighed against systemic chemotherapy.

Introduction

The appendix vermiformis is commonly regarded as the organ that will introduce a surgical trainee to the art of his or her chosen specialty. Inflammation of this organ, namely appendicitis, is the disease process which will be instrumental in "teaching" the fundamentals of history taking, physical examination and differential diagnosis of the acute abdomen to medical students and surgical residents. Appendectomy is the most frequent emergency operation

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Table 37-1. Clinical scenarios depending on type and timing of diagnosis of appendiceal neoplasms

Scenario	Acute symptoms	Presumptive preoperative diagnosis	Surgery	Pre-/intraop evidence of perforation (P) or dissemination (D)	Timing of tumor recognition	Impact/action in decision-making
1. Acute	Y	Appendicitis	N	–	N	Rely on indirect signs/risk factors for identification of affected individuals
						Re-imaging?
2. Acute	Y	Appendicitis	Y	P–	(a) Intraoperative	Primary or secondary evaluation for more extensive/oncological surgery/treatment
				D–	(b) Only on final pathology	
					(c) Not recognized at all (missed opportunity)	
3. Acute	Y	Appendicitis	Y	P+	(a) Intraoperative	Appropriate treatment for perforation with primary or secondary evaluation for more extensive/oncological surgery/treatment
				D–	(b) Only on final pathology	
					(c) Not recognized at all (missed opportunity)	
4. Acute	Y	Appendicitis	Y	P+	Intraoperative	Primary appropriate treatment for perforation
				D+		Secondary assessment for more extensive surgery/treatment
5. Acute	Y	Appendicitis	Y	P–	Intraoperative: evidence of localized mucocele or tumor involving the appendix/cecum	Intraoperative determination of appropriate extent of resection
				D–		Possible frozen section
6. Elective	Y/N	Localized mucocele/tumor involving appendix/cecum—no signs of PMP	Y	P–	Preoperative	Oncological resection
				D+		Preparedness for HIPEC
7. Elective	Y/N	Localized mucocele/tumor of appendix/cecum AND signs of PMP	TBD	P–	Preoperative	PCI
				D+		Systemic treatment and evaluation for CRS/HIPEC
8. Elective	Y/N	PMP, but no obvious cecal pathology	TBD	P–	Preoperative	Evaluation for other potential primary tumor locations
				D+		PCI
						Systemic treatment and evaluation for CRS/HIPEC
9. Elective	Y/N	PMP+distant metastases	N	P–	Pre-treatment	Systemic treatment
				D+		

performed by general surgeons with close to 300,000 performed in the United States annually [1, 2], of which a substantial proportion are performed laparoscopically. On comparably rare occasion, the pathology of the appendectomy specimen incidentally reveals an appendiceal neoplasm ("incidentaloma"), which sometimes is recognized even before or at least during surgery, but more often only after the patient has already been discharged from the hospital. Paradoxically and despite the fact that abdominal surgeons at all levels are very frequently involved in treating appendiceal pathology, appendiceal neoplasms are quite infrequent but may cause rather complex intellectual, management and technical challenges in subsequent surgical interventions (Table 37-1) [3].

Epidemiology

Primary neoplasms of the appendix have an incidence of 0.12 cases per 1,000,000 person years and are found in 0.9–1.4% of appendectomy specimens [3, 4]. They can be asymptomatic, be associated with appendicitis, or cause noninflammatory symptoms. Preoperative diagnosis based on symptoms, imaging, and laboratory results is extremely rare. Even intraoperatively, less than 50% appendiceal neoplasms are recognized as such. A retrospective cohort analysis of the Surveillance, Epidemiology, and End-Results database suggested that the incidence of appendiceal neoplasms has increased significantly in the past few decades from 0.63 to 0.97 per 100,000 population [5, 6]. It is unclear

Table 37-2. Reported incidence over time of appendiceal neoplasms in SEER database [5, 6]

Subtype	1973–2001 (*N*=2514)	2000–2009 (*N*=4765)
Mucinous adenocarcinoma (%)	38	38
Non-mucinous adenocarcinoma (%)	26	27
Carcinoid tumors (%)	17	28
Goblet cell carcinoids (%)	15	
Signet ring cell tumors (%)	4	7

Table 37-3. Tumor classifications and manifestations

	Localized[a]	Disseminated	Pattern of dissemination[b]
Epithelial	Adenoma (B)		L, H, P
	Adenocarcinoma (M)	Adenocarcinoma	L, H, P
	Mucocele (B)	PMP: Mucinosis peritonei	P
	Mucinous cystadenoma (IM, LAMN)	PMP: Disseminated peritoneal adenomucinosis (DPAM)	P
	Mucinous (cyst-)adenocarcinoma (M)	PMP: Peritoneal mucinous adenocarcinomatosis (PMAC)	P, L, H
		PMP: Peritoneal mucinous carcinomatosis (PMCA)	P, L, H
	Signet ring cell carcinoma (M)	Advanced/metastatic signet ring cell carcinoma	DI, P, L, H
Mixed	Goblet cell carcinoid (adenocarcinoid)	Metastatic goblet cell adenocarcinoid	P, L, H
Non-epithelial	Carcinoid	Metastatic carcinoid	L, H
	<1 cm (B)		
	1–2 cm (IM)		
	>2 cm (M)		
	Lymphoma (M)	Disseminated/multicentric lymphoma	Systemic
	Leiomyoma (B)		
	Leiomyosarcoma (M)	Metastatic leiomyosarcoma	H, L
	Kaposi sarcoma (M)	Disseminated Kaposi sarcoma	Systemic

LAMN Low grade mucinous neoplasia, *PMP* Pseudomyxoma peritonei
[a]*B* Benign, *IM* Intermediate malignant potential, *M* Malignant
[b]*P* Peritoneal, *L* Lymphatic, *H* Hematogenous, *DI* Diffuse infiltrative

though whether this is a true increase or a simple reflection of higher awareness and reclassification as a separate entity. The increase appears to have affected all histological subtypes in an equal fashion (Table 37-2) [5, 6]. Historically, carcinoid tumors were considered the most frequent neoplasms originating within the appendix, and in 1955 a systematic evaluation of 50,000 appendectomy specimens revealed only 41 epithelial neoplasms (0.082%) [7]. More recent publications, however, demonstrate that epithelial neoplasms are more frequent and represent 58% of malignant appendiceal tumors [5, 8]. At the same time, a surge was also noted for the frequency of distant metastatic disease [5]. In contrast, however, appendiceal carcinoids have an incidence of 0.15/100,000/year but the relative frequency compared to other primary sites of neuroendocrine tumors within the gastrointestinal tract has decreased to 16.7% [9, 10]. Epithelial appendiceal neoplasms—paralleling colorectal cancer—usually develop in the sixth or seventh decade of life, whereas non-epithelial pathology including neuroendocrine tumors occur at a younger age, namely the fourth to fifth decade [2, 5, 7, 8, 11]. At the time of diagnosis, a total of 74% of appendiceal cancer cases have already spread, and developed regional or distant metastases in 39% and 35%, respectively [5].

Anatomical Pathology and Staging

The literature unfortunately has for a long time shown little consistency and used a variety of nomenclatures, classification systems, and descriptive terms when referring to appendiceal neoplasms. The many synonyms for lesions of such rarity undoubtedly has led to confounding terminology. From an anatomical point of view, the appendix in essence has a smaller diameter but otherwise a similar layered wall structure as the rest of the large intestine; however there is a higher representation of immunological tissue components (GALT, gut associated lymphoid tissue). The appendix does not participate in processing of intestinal contents but produces 2–3 mL of mucin per day and may participate in immunological functions. The arterial blood supply originates from the appendicular artery which branches off the ileocolic artery; the venous drainage is via the superior mesenteric vein to the portal vein system; the lymphatic drainage follows the vascular structures and due to variability may parallel the ileocolic, right colic, and right branch of the middle colic artery.

Appendiceal neoplasms should be categorized according to the tissue of origin as well as the pattern of growth, expansion, and spreading (Table 37-3). As for the latter,

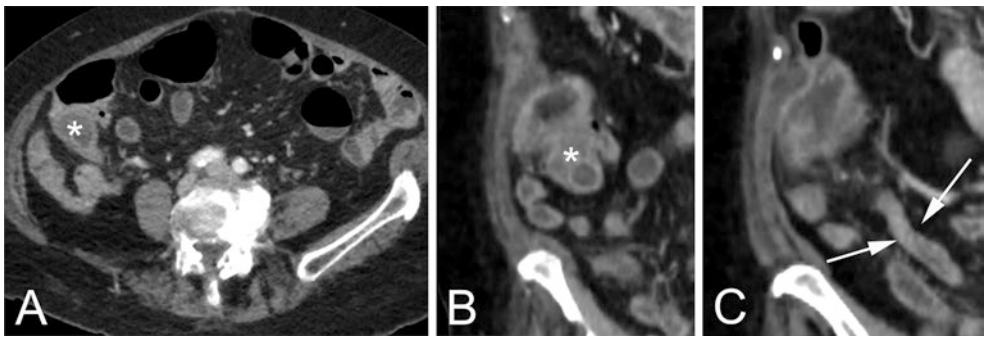

FIGURE 37-1. Appendiceal mucocele: the computed tomography shows the cystic enlargement at the base of the appendix (*asterisk*, panels (**a**) and (**b**)), as well as the moderately enlarged appendix (in-between *arrows*, panel (**c**)).

tumors may either metastasize via vascular, lymphatic, or transperitoneal route. A major distinction is made between epithelial and non-epithelial lesions, the latter of which includes among others neuroendocrine tumors such as carcinoid tumors.

Epithelial Neoplasms

Epithelial neoplasms are divided into mucinous and non-mucinous neoplasms [8]. Mucinous neoplasms of the appendix are classified according to the grade and aggressiveness of the tumor. Descriptively, these lesions characteristically can form mucoceles of the appendix, a morphologic term describing the dilation of the appendix with intraluminal accumulation of mucoid material (Figure 37-1). The obstruction can either be caused by the epithelial neoplasm itself, an independent tumor, or a benign process (retention cysts, mucosal hyperplasia). Rupture of a mucocele results in peritoneal spillage and spread of mucin and—depending on the malignant potential of the lesion—of cellular elements, which are the basis for mucinosis, pseudomyxoma peritonei, and carcinomatosis.

Low grade appendiceal mucinous neoplasms (LAMN) are well-differentiated neoplasms that morphologically resemble adenomas. LAMN has become the neutral term for a number of entities such as appendiceal villous or serrated adenoma, cystadenoma, borderline tumor of the appendix, and mucinous tumors of uncertain malignant potential. These lesions tend to grow slowly and grossly are characterized by a well-defined structure, cystic dilation, and mucinous content. The appendiceal wall is fibrotic and—as a sign of chronicity—may sometimes contain calcifications. Gross rupture (spontaneously or as a result of surgical manipulation) may be evident as mucin extruding on to the serosal surface or seeding of more distant peritoneal surfaces as evidenced by presence of mucin lakes. Histologically, the appendiceal mucosa is replaced by adenomatous proliferations of villous, papillary, serrated, or flat mucinous character. The columnar epithelial cells are mucin-rich and may have elongated (pencil-shaped), mildly hyperchromatic nuclei with nuclear pseudostratification, rare mitoses, and apoptotic nuclear debris. It is of note that the neoplastic epithelium on occasion may herniate through the muscularis propria and form "pseudodiverticula." One might speculate that these extensions represent a route by which such lesions perforate and disseminate to the peritoneal cavity [11].

Prognosis of LAMN depends on the presence or absence of epithelial cells outside the appendix. Tumors confined to the appendix generally have an excellent prognosis. However, LAMN may proliferate outside the appendix in a malignant fashion, producing pseudomyxoma peritonei and/or distant metastases. Pseudomyxoma peritonei (PMP) derived from perforation of a LAMN is characterized by abundant extracellular mucin, hyalinized fibrotic stroma, and harboring scant strips of low-grade mucinous epithelium [8]. The term is not strictly limited to appendiceal neoplasms but the condition can result from other tumor origins such as ovaries, gallbladder, and others. The prognosis of a ruptured LAMN is dependent on the amount and cellularity of mucin deposits, and recurrence rates increase when epithelial cells are present in the mucin. Most instances of PMP resulting from LAMN remain confined to the right lower quadrant. Even if the spread of PMP goes beyond the immediate vicinity, the lesion may pursue an indolent but progressive course. The superordinate term "PMP" has been categorized into disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous (adeno-) carcinomatosis (PMAC or PMCA) [12]. The former reflects a low-grade pseudomyxoma arising from LAMNs, whereas the latter indicates peritoneal carcinomatosis. DPAM lesions contain scarce strips of low-grade mucinous epithelium with mild atypia and no significant mitotic activity; [12] these low-grade lesions usually cover but do not infiltrate the surface of the organs to which they adhere.

Appendiceal adenocarcinoma is also divided into mucinous and non-mucinous types. Mucinous adenocarcinoma of the appendix is characterized by a destructive growth pattern with tumor invasion of the appendiceal wall beyond the muscularis mucosae; infiltrating pools of mucin harbor cytologically malignant glandular epithelium arranged in strips, clusters,

and complex proliferations. Mucinous adenocarcinoma due to the increasing pressure of accumulating mucin is prone to rupture, spreading, and seeding into the peritoneal cavity, leading to formation of pseudomyxoma peritonei. Mucinous tumors spread along peritoneal surfaces, even in the absence of lymph node metastases. Peritoneal mucinous (adeno-)carcinomatosis (PMAC/PMCA) results from secondary peritoneal proliferation of appendiceal or intestinal mucinous adenocarcinoma nests that lead to invasion of parenchymal and visceral organs and the omentum, and potentially trigger secondary lymph node metastases at those sites.

Non-mucinous adenocarcinomas behave similarly to colonic adenocarcinomas, infiltrating the appendiceal wall and metastasizing to regional lymph nodes and the liver [11]. Non-mucinous adenocarcinomas show a spectrum of morphological features of the invasive component. In some cases the tumor is identical to colonic adenocarcinoma with malignant (pseudo-)glandular formations, increased stratification, and disorganization (compared to the regular columnar epithelium). In other cases, the malignant glands are tubular in shape, lined by cuboidal epithelium, associated with modest amount of extracellular mucin.

Signet-ring cell carcinoma is a rare but aggressive subentity of mucinous adenocarcinoma, characterized by dissolute growth and infiltration of mucin-containing cancer cells (signet rings); it almost never remains confined, may display an infiltrative growth below intact appearing mucosal surfaces as well as a rapid dissemination within the peritoneal cavity. Signet-ring cell carcinoma is typically associated with a poor prognosis.

Prognosis of appendiceal adenocarcinomas—similar to colon cancer—is primarily determined by the stage, but within stage IV also depends on the histological subtype and grading as well as the route of dissemination. Within each stage and histological subtype, poor differentiation is associated with unfavorable outcomes. Mucinous adenocarcinomas have a markedly worse outcome (reduced cancer-specific survival) than non-mucinous adenocarcinomas of the appendix (Table 37-4). This observation, which was based on published data analysis of the National Cancer Database (NCDB) [4], was recently implemented into the current staging guidelines by the American Joint Commission for Cancer (AJCC) [13]. Appendiceal carcinomas for the first time are classified separately from colonic adenocarcinoma, and distinction is made between mucinous and non-mucinous types; histologic grading for mucinous tumors is considered of particular importance for metastatic tumors (Table 37-5). Stage T4 is divided into T4a (penetration of visceral serosa) and T4b

Table 37-4. Cancer-specific survival for appendiceal adenocarcinoma stratified by stage and grade [4]

Subtype	Stages I–III (%)	Stage IV (%)
Mucinous adenocarcinoma ($N=1375$)		
Well differentiated	82	71
Moderately differentiated	64	51
Poorly differentiated	50	0
Non-mucinous adenocarcinoma ($N=860$)		
Well differentiated	69	48
Moderately differentiated	73	9
Poorly differentiated	55	5

Table 37-5. TNM staging by AJCC for appendiceal adenocarcinoma [13]

Stage	T	*N*	M
X	Primary tumor not determined, or any T	Regional lymph nodes not determined, or any *N*	Metastatic disease not determined, or any M
0	No evidence of primary tumor	No regional lymph node metastasis	No distant metastasis
Is	Carcinoma in situ: intraepithelial or invasion of lamina propria	–	–
1	Tumor invades submucosa	Metastasis in 1–3 regional lymph nodes	1a: Intraperitoneal metastasis beyond the right lower quadrant, including pseudomyxoma peritonei
			1b: Non-peritoneal metastases
2	Tumor invades muscularis propria	Metastasis in four or more regional lymph nodes	
3	Tumor invades through muscularis propria into subserosa or into mesoappendix		
4	4a: Tumor penetrates visceral peritoneum, including mucinous peritoneal tumor within the right lower quadrant		
	4b: Tumor directly invades other organs or structures		

Stage I: T1–2 N0 M0; stage II: T3–4 N0 M0; stage III: Tx N1–2 M0; stage IV: Tx Nx M1

(invasion of other organs). In mucinous tumors that penetrate the visceral peritoneum and cause mucin deposits confined to the right lower quadrant are still considered a T4a (that is a stage II if no lymph nodes are involved); when mucin has dispersed beyond the right lower quadrant, it is designated M1a (stage IV) [13]. M1 is divided into M1a and M1b to distinguish pseudomyxoma peritonei (M1a) from nonperitoneal metastasis (M1b) [13].

Neuroendocrine Appendiceal Lesions/ Carcinoid Tumors

The WHO classification utilizes the terms "neuroendocrine tumor" (NET), "neuroendocrine carcinoma" (NEC), and "mixed adeno-neuroendocrine carcinomas" (MANEC) [14]. Synonyms for NET include carcinoid tumors and well-differentiated endocrine tumors/carcinoma. Synonyms for NEC: poorly differentiated endocrine carcinoma and small cell/large cell endocrine carcinoma. Goblet cell carcinoids (now called carcinomas) are MANEC [14].

Carcinoids or carcinoid tumors represent NETs grade 1 and derive from a variety of dispersed neuroendocrine cells (formerly labeled as amine precursor uptake and decarboxylation cells, APUD cells). These cells and the resulting tumors are not only found in the appendix but also in the entire gastrointestinal tract and other organs and are therefore addressed more comprehensively in the next chapter. Nonetheless, appendiceal carcinoids are only extremely rarely associated with multicentricity, and there is no known association with multiple endocrine neoplasia (MEN syndrome).

Appendiceal carcinoids belong to the embryological and anatomical region of the midgut to include jejunum, ileum appendix, cecum, and right colon. More than foregut and hindgut carcinoids, these midgut carcinoid cells characteristically are hormone-active. Among other products (such as GH, GHRH, gastrin, calcitonin, substance P, insulin, and neurotensin), they produce serotonin from its precursor 5-hydroxytryptophan by means of the enzyme aromatic acid decarboxylase; serotonin is subsequently metabolized in the liver by monoamine oxidase to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine.

On gross examination, carcinoid tumors of the appendix are yellow-tan firm nodules. 75% are located at the tip, 15% in the mid-appendix and 10% at the base of the organ. At the time of diagnosis, the majority (80%) is less than 1 cm, 14% measure between 1 and 2 cm, and 6% are greater than 2 cm in size [14]. Histologically, carcinoids are characterized by submucosal uniform cell conglomerates with a nested or insular pattern. The cytoplasm has a modestly eosinophilic, fine granularity, and the nuclei show the classic endocrine "salt-and-pepper" chromatin pattern. Tumors have positive reactions to silver stains (argentaffin/argyrophilic) and immunohistochemically to markers of neuroendocrine tissue, including neuron-specific enolase, synaptophysin, and chromogranin A [11]. Ki67 is used to determine the proliferative capacity of the tumor for grading according the current WHO classification [14, 15]. Under the electron microscope (which is not part of routine examinations), carcinoid tumors are typically found to contain numerous membrane-bound neurosecretory granules which store a variety of hormones and biogenic amines [16].

With increasing size of the lesion, the tumor may extend deeper into the wall and even reach the peritoneal surface or in up to 27% of cases infiltrate the mesoappendix. Hence, the AJCC staging for carcinoids is based on tumor size as it correlates with the incidence of metastases and represents the most important prognostic parameter, whereas depth of invasion, lymphatic, perineural, or serosal invasion lack prognostic power (Table 37-6). Lymph node metastases are

Table 37-6. TNM staging (by AJCC and ENETS) for neuroendocrine appendiceal tumors [15]

Stage	T (AJCC)	T (ENETS)	*N* (AJCC/ ENETS)	M (AJCC/ ENETS)
X	Primary tumor not determined, or any T	Primary tumor not determined, or any T	Lymph nodes not determined, or any *N*	Metastatic disease not determined, or any M
0	No evidence of primary tumor	No evidence of primary tumor	No lymph node metastasis	No distant metastasis
1	1a: Tumor ≤1 cm 1a: Tumor 1–2 cm	T1 Tumor ≤1 cm invading submucosa and muscularis propria	Lymph node metastasis	Distant metastasis
2	Tumor 2–4 cm or with extension to the cecum	Tumor ≤2 cm with invasion of submucosa or muscularis propria, and/or minimal invasion (up to 3 mm) of subserosa/ mesoappendix		
3	Tumor >4 cm or with extension to the ileum	Tumor >2 cm and/or extensive invasion (>3 mm) of subserosa/mesoappendix		
4	Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle[a]	Tumor invades peritoneum/other organs		

[a]Tumor adherent to other organs or structures grossly classified as cT4 but if microscopically negative adhesion as pT1–3 depending on depth of wall invasion

Stage I: T1 N0 M0; stage II: T2–3 N0 M0; stage III: T4 N0 M0 or Tx N1 M0; stage IV: Tx Nx M1

Table 37-7. Impact of appendiceal carcinoid size on lymph node metastasis and survival [11, 14, 18, 49]

Carcinoid size	LN metastases (%)	5–/10-Year survival rates (%)
<1 cm	<1.0–15.0	92–100
1–2 cm	3.0–47.0	81
>2 cm	20–86	31

rare for lesions of less than 10 mm diameter, but occur in 20–30% of patients with carcinoids greater than 2 cm in size (Table 37-7); distant metastases are comparably rare in appendiceal carcinoids. It should be noted that the staging system by the European Neuroendocrine Tumor Society (ENETS) differs from AJCC as it also takes into account depth of appendiceal wall and meso-appendiceal invasion with invasion greater than 3 mm representing more aggressive disease [17]. Five-year survival rates for patients with local, regional metastatic, and distant metastatic disease are 95%, 81%, and 31%, respectively [9, 15, 18].

Goblet Cell Carcinoids

This term may add confusion to the classification of appendiceal lesions. It is considered a hybrid between epithelial and NETs and is also referred to as mucinous adenoneuroendocrine carcinoma [19–21]. These tumors have a mean age of presentation in the fifth decade and behave more like adenocarcinoma than carcinoid. Clinically, goblet cell carcinoids in the middle third of the appendix may in fact cause appendicitis [22]. At surgical exploration, 10% or more of the tumors are found to have already widespread metastatic disease; two-thirds of goblet cell carcinoids are incidental findings on appendectomy and ileocecectomy specimens. Five-year survival rates are worse than for regular carcinoids and for stages I, II, III, and IV were 100%, 76%, 22%, and 14%, respectively, i.e., range from 50 to 80% for locoregional disease to less than 20% for patients with distant metastases [19, 20].

Rare Appendiceal Neoplasms

All other neoplasms are comparably rare and often represent a more systemic disease process. Among the rarities, primary lymphoma of the appendix is seen with some frequency; it affects patients of all ages but most frequently occurs in the second to fourth decade of life. In children and young adults, Burkitt's lymphoma is the most common subtype, whereas older patients are more likely to have diffused large B-cell lymphoma. Furthermore, the appendix has been reported as the site of relapse of several subtypes of lymphoma [11]. Any of these lesions may either present with acute appendicitis or through a palpable mass, intussusception, or lower gastrointestinal bleeding as rarer manifestations. Other even less common and therefore not further detailed lesions include Kaposi sarcoma, leiomyoma or leiomyosarcoma, or leukemic infiltrates.

Clinical Features

Appendiceal epithelial neoplasms are notorious for the absence of any specific signs or symptoms, especially at early stages. Complicating factor is that they escape detection by routine screening efforts such as colonoscopy [23]. If a tumor is concentric and causes obstruction of the lumen, clinical symptomatology of appendicitis may ensue. Red flags in patients with signs of "appendicitis" should include any age above 50, family history of colorectal cancer or inflammatory bowel disease, prolonged history, or anemia. At later stages, epithelial appendiceal neoplasms may present as a localized abdominal or pelvic mass, bowel obstruction, or as progressive, painless, abdominal distention when large volumes of mucin accumulate in the peritoneal cavity (pseudomyxoma peritonei) [2–5].

Even hormone-active tumors such as carcinoids remain silent and are only incidentally detected. Since they are frequently located at the tip of the appendix, they may not even trigger appendicitis. Carcinoid syndrome or "crisis" with flushing, wheezing, diarrhea, and eventually right-sided valvular heart disease results from the release of serotonin and other vasoactive substances. From appendiceal primary carcinoids, this is extremely rare (less than 5%) and requires presence of significant metastatic disease to allow these substances to escape the hepatic first-pass effect and be released into the systemic circulation.

Given the incredible variability of clinical circumstances under which an appendiceal neoplasm may be diagnosed, clinicians will have to develop concepts and algorithms to optimize and standardize their management (Table 37-1).

Diagnostic Procedures

Clinical examination is expectedly unreliable in detecting, confirming, or ruling out an appendiceal neoplasm. Tumor markers are limited and include nonspecific carcinoembryonic antigen (CEA) for epithelial lesions, or 5-HIAA metabolites in the urine for carcinoids. Neither marker is suited for screening or as a negative predictive test. Cross-sectional imaging (CT, MRI) is of greatest value in evaluating a suspected appendiceal neoplasm. Plain radiographs or contrast small bowel follow-throughs may suggest a mass effect when adjacent loops of bowel appear to be displaced, but are rarely definitive. Similarly, contrast enemas, even though rarely done, may provide a hint of an extrinsic impression on the cecum, terminal ileum, or sigmoid colon.

Ultrasonography in skilled hands may allow for identification of appendiceal abnormalities, including appendicitis, fecoliths, mucoceles (hypoechogenic structure), or on occasion a mass in the right lower quadrant. Cystic masses may have a heterogeneous appearance due to the combination of fine cellular framework with mucin-containing chambers with synchronously liquid, gelatinous, and viscous components. A lack of appendiceal wall thickening (>6 mm) suggests

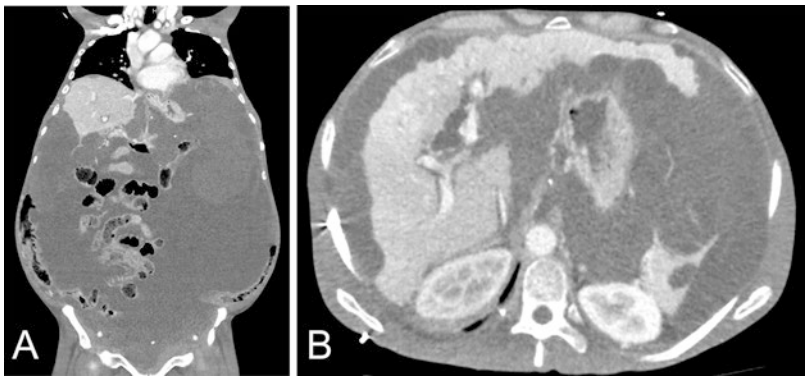

FIGURE 37-2. Pseudomyxoma peritonei: the computed tomography a coronal view (panel (**a**)) and axial view (panel (**b**)) of a patient with massive deposits of low attenuation mucin throughout the entire abdomen with scalloping of the liver contour and widening of the spaces between the compressed bowel loops.

absence of inflammation (appendicitis). A target sign either implies an enlarged and edematous appendix or an intussusception. To a limited degree, mucinous ascites can be detected and even quantified, but for comprehensive assessment of pseudomyxoma, ultrasound is not well suited.

CT or, less commonly used, MRI are the cross-sectional imaging modalities of choice as they provide reproducible, complete, and quantifiable evaluation of the whole abdomen [24, 25]. They are indicated for workup of right lower quadrant symptoms, or after the fact when diagnosed tumors (epithelial and non-epithelial) require lymph node and systemic staging, treatment planning, or evaluation of treatment response. Tumors of sufficient size can be demonstrated as a moderately enhancing soft tissue mass or a cystic dilatation of the appendix beyond 15 mm, which should raise suspicion if noted as an incidental finding [26]. Bowel displacement is an indirect sign of a pathological extraluminal process and is best visualized by adequate opacification of the terminal ileum and cecum by means of intraluminal contrast and differs from an abscess by the lack of inflammatory signs. Features of a mucocele include well-encapsulated and smooth lesions in the right lower quadrant with regular wall and low attenuation that depends on the amount of mucin in the tissue and the center of the lesion [27]. Presence of punctuate, curvilinear calcifications in a right lower quadrant cystic lesion are highly suggestive of a mucocele: they develop as a dystrophic response to a chronic inflammatory process. Myxoglobulosis is an anecdotal variant of an appendiceal mucocele with formation of multiple translucent or calcified mucin globules rather than a homogenous mucin lake.

Pseudomyxoma peritonei is characterized by low attenuation ascites and serosal implants which when not obvious are best seen as scalloping of the liver contour, at peritoneal reflections, or the pouch of Douglas (Figure 37-2). For treatment strategy and prognosis, it is important to quantify areas affected by PMP. The peritoneal carcinomatosis index (PCI) is a summary score with a maximum of 39 points from nine abdominal squares and 4 small bowel segments, whereby each area is scored between 0 and 3 when deposits are >5 cm [24]. Positron emission tomography (PET scan) may have a role for detection or monitoring of systemic metastatic disease but is notoriously ineffective in assessing pseudomyxoma peritonei.

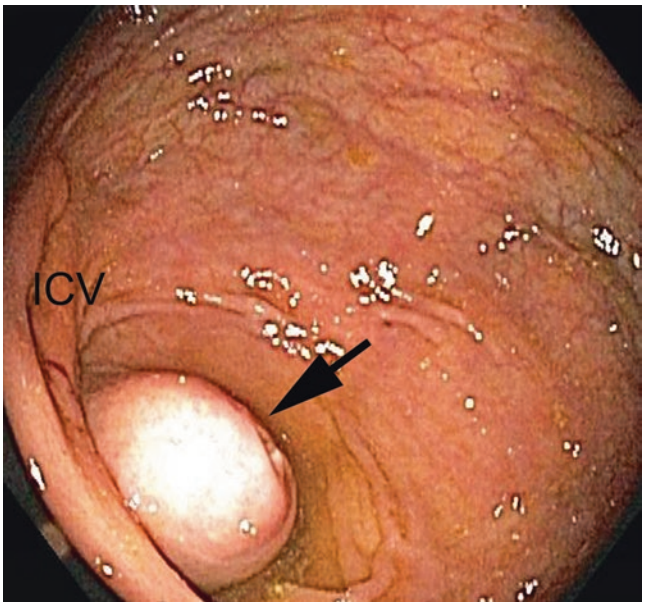

FIGURE 37-3. Colonoscopic appearance: even though appendiceal neoplasms frequently escape endoscopic detection, they occasionally lead to an extramucosal protrusion (*asterisk*) of the appendiceal orifice into the cecal lumen. ICV: ileocecal valve.

Since most carcinoids are surgical/pathological incidentalomas, most diagnostic investigations are performed after the initial operation. For the majority of incidentally diagnosed, well-differentiated appendiceal NERs of <10 mm, no postoperative diagnostic procedure is necessary [15]. After complete resection of 10–20 mm lesions, a single CT or MRI to rule out lymph node and distant metastases is recommended, but without level I evidence [15]. For lesions >20 mm, CT and or MRI of the abdomen is recommended; in addition a PET scan or a somatostatin receptor scan in combination with SPECT/CT (or Somatostatin Receptor PET with 3-phase CT scan) may be considered to detect or rule out distant tumor spread.

Appendiceal neoplasms typically evade detection by colonoscopy [23]. Occasionally, a protrusion of the appendiceal orifice or release of mucoid material may be recognized (Figure 37-3). However, colonic evaluation (colonoscopy, CT

colonography) is recommended prior to any elective intervention for a suspected or proven appendiceal neoplasm, because both epithelial and NETs may be multicentric and/or be associated with a synchronous lesion in up to 10–20% [28].

Medical Management

Management of localized appendiceal neoplasms is primarily surgical. Nonsurgical modalities come into play for locally advanced or metastatic lesions as well as for primarily systemic neoplasms such as leukemia or lymphoma. Pseudomyxoma of too significant extent (high PCI) may not benefit from cytoreductive surgery and HIPEC (see later). Adjuvant and palliative systemic chemotherapy are still largely based of 5-fluorouracil and typically combined with other conventional agents (oxaliplatin and others), or biological drugs such as bevacizumab [29]. Regimens and timings before, during and after surgery remain areas of research [30, 31]. Somatostatin is being used for metastatic and particularly symptomatic carcinoid tumors. Radiation treatment is not part of routine management of any appendiceal tumor and is reserved for special circumstances on an individualized basis.

Surgical Treatment of Appendiceal Lesions

Surgery is the primary treatment for localized disease with the goal to achieve a curative R0 resection; in metastatic disease, the role of surgery needs to be individually analyzed and weighed against systemic chemotherapy or best palliative care. Surgical decision-making should therefore take five questions into consideration as also alluded to in the previously listed clinical scenarios:

1. Has the primary tumor already been removed?
2. Was the clinical situation associated with possible tumor spillage?
3. For a given tumor, what entails an adequate margin?
4. What is the probability of nodal involvement?
5. In case of locally advanced or metastatic disease, is aggressive surgical intervention superior to conservative management?

Depending on the answers, there are four possible surgical responses (Table 37-8): (a) appendectomy only, (b) hemicolectomy or completion hemicolectomy, (c) cytoreductive surgery and peritonectomy with or without HIPEC, or (d) conservative management.

Appendectomy

Appendectomy alone should be reserved for premalignant lesions, carcinoma in situ (Tis), or carcinoids of less than 1 cm diameter provided that a sufficient margin can be obtained. Carcinoids of 1–2 cm represent a grey zone but may be associated with a higher than previously reported incidence of nodal disease [18], suggesting that appendectomy may not suffice. An appendiceal mucocele requires careful dissection to avoid perforation of the lesion. If the case is approached laparoscopically, placement of the whole appendix/cecum into a specimen bag prior to starting the dissection may be a strategy to avoid rupture and spillage or conversion to a laparotomy [32].

TABLE 37-8. Operations performed for appendiceal neoplasms

Appendectomy	Right hemicolectomy	Cytoreduction + HIPEC	Nonsurgical
Intact mucocele	Invasive adenocarcinoma	PMP with PCI ≤16 (–20):[a]	PMP with PCI > (16–)20?[a]
Adenocarcinoma tis		– Diffuse mucinous adenomucinosis peritonei	Adenocarcinoma with diffuse systemic metastases
		– Peritoneal mucinous (adeno-) carcinomatosis	Adenocarcinoma with peritoneal disease AND systemic metastases
		Perforated appendiceal neoplasm without visible PMP?	
Appendiceal carcinoid <1 cm, R0	Appendiceal carcinoid 1–2 cm, R0?		Carcinoid with diffuse systemic metastases beyond one organ
	Appendiceal carcinoid >2 cm		
	Any carcinoid with insufficient margin (R1, questionable R), multifocality, invasion of mesoappendix >3 mm		
	Any carcinoid with nodal involvement		
	Any carcinoid with systemic metastases to the liver only		
	Goblet cell carcinoid	PMP from goblet cell carcinoid	Widespread systemic metastases, or PMP from goblet cell carcinoid with systemic metastases

[a]*PMP* Pseudomyxoma peritonei, *PCI* Peritoneal carcinomatosis index

Right Hemicolectomy

For non-perforated appendiceal adenocarcinoma, carcinoids larger than 2 cm and any of the previously mentioned lesions with unfavorable features or whose margins are insufficient with an appendectomy alone, an oncological right hemicolectomy with a mesocolic lymph node dissection is indicated [15, 18]. Oncological resection for adenocarcinoma achieves better 5-year survival rates than appendectomy alone [33]. The incidence of lymph node metastases in appendiceal carcinoid tumors increases with size of the tumor (Table 37-7). There is controversy regarding the surgical management of patients in which perforation of a mucinous appendiceal neoplasm has occurred resulting in pseudomyxoma peritonei. Some argue that a right hemicolectomy is not necessary in this situation as the outcome is determined by the peritoneal disease rather than the lymph nodes [32, 34].

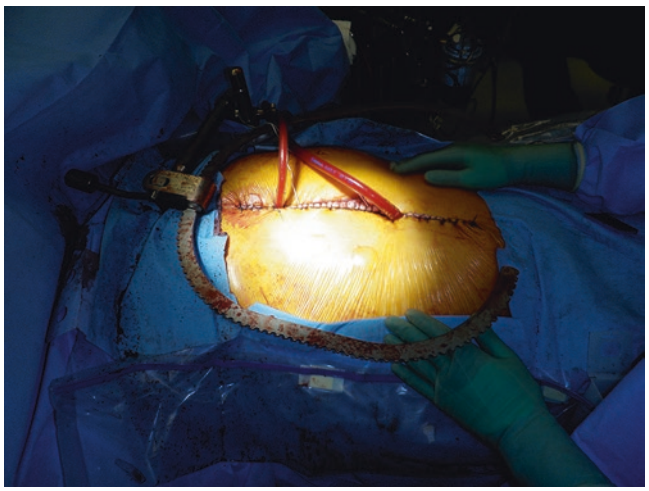

FIGURE 37-4. Hyperthermic intraperitoneal chemotherapy (HIPEC) (Courtesy of Eric K. Johnson, M.D.).

Cytoreductive Surgery and HIPEC

In cases of advanced peritoneal dissemination, cytoreductive surgery with HIPEC is performed in selected cases [15]. If pseudomyxoma peritonei is unexpectedly encountered during an operative exploration, the patient would be best served by careful retrieval and cytological analysis of any mucinous fluid present, and referral to a specialized center with expertise in cytoreductive surgery and HIPEC [35]. Minimization of surgical manipulation and mobilization of intra-abdominal viscera will facilitate the subsequent cytoreductive surgery performed later.

The mainstay of surgical treatment for disseminated peritoneal disease is the arduous operative task of cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) (Figure 37-4). In retrospective series, this surgical modality has demonstrated favorable results in carefully selected patients [36], but at the same time was associated with a substantial morbidity and mortality; [37–41] in addition, most series note that incomplete cytoreduction was unable to achieve a relevant benefit as the recurrence rates were very high [37, 42, 43]. It seems rather obvious that the outcomes depend on the extent of the initial disease whereby a number of authors recommended to limit cytoreductive surgery and HIPEC to patients with a PCI of less than (16–)20.

In reviewing the evidence supporting the use of cytoreduction and HIPEC, it should be noted that the literature on the technique and outcomes continues to have significant limitations. On one hand, most series are retrospective and inconsistent in regards to inclusion criteria, extent of disease, concomitant treatment, protocols, and follow-up. Selection bias is inherent to their study designs. Furthermore, they are heavily dominated by Sugarbaker [44], who has advocated for the use of cytoreduction and HIPEC not only for appendiceal neoplasms, but also for peritoneal carcinomatosis arising from non-appendiceal cancers. Corroboration of his data by other groups is in process, but at the same time challenged by availability of more aggressive systemic chemotherapy regimens, the latter of which parenthetically has been found to increase the risk of complications after HIPEC [31]. Most importantly, however, there is a lack of prospective randomized data on direct comparison of HIPEC and cytoreductive surgery with systemic chemotherapy alone. The only prospective randomized trial to date that suggested improved outcomes with HIPEC compared to systemic treatment only was limited by a chemotherapy regimen (fluorouracil-leucovorin) that many feel was not representative of modern treatment standards [43]. A heated debate continues as to whether HIPEC should be considered the standard of care or still an experimental approach [45, 46].

In preparation for cytoreductive surgery and HIPEC, adequate staging and quantitative assessment using the PCI [24], colonic clearance, aggressive hydration, and bowel cleansing are essential. Considerations include provisions for stomas, timely prophylactic vaccination for splenectomy (against pneumococcus, meningococcus, and H. Influenza) and placement of a gastrostomy tube and feeding jejunostomy tube. Cytoreductive surgery aims at removing or reducing all visible tumor implants to less than 2 mm in size as only complete cytoreduction allows for adequate drug penetration into residual tumor deposits. It typically includes omentectomy and stripping of all parietal peritoneal surfaces, including the subdiaphragmatic spaces and the paracolic recesses (peritonectomy). However, it may also involve aggressive multiorgan resection including tumor-involved bowel (colon, small bowel) or other organs (gallbladder, spleen, uterus/ovaries, and others) or the posterior rectus sheath may be removed. For the HIPEC phase of the procedure, a number of open or closed techniques have been reported. We have typically used the closed technique to minimize heat dissipation, spillage of perfusate, and safety hazard to health personnel [47, 48]. The incision is temporarily closed to the size of a gel port through which large-bore afferent and efferent cannulas are placed to the peritoneal cavity. The heated chemothera-

Table 37-9. Selected series on cytoreductive surgery and HIPEC for appendiceal neoplasms

Institution	Year	*N*	Appendiceal origin (%)	Complete CR[a] (%)	M/M[b]	RR[c]	SV[d]
Washington Cancer Institute [50]	1999	200	75	n/a	27/2	n/a	n/a
University of Cincinnati College of Medicine [51]	2004	33	67	67	27/0	>33	(49)[e] (3 years)
Wake Forest University, NC [52]	2006	110	100	28	38/4	n/a	53.4 (5 years)
Istituto dei Tumori, Milan, Italy [53]	2008	96	100	67	27/1	61	71.9 (5 years)
Washington Cancer Institute [54]	2008	472	85	100	n/a	26	n/a
Mercy Medical Center, Baltimore MD [55]	2012	77	100	65	27/0	n/a	40 (3 years)
International Multicenter [36]	2012	2298	100	51	24/2	n/a	63 (10 years)
National Cancer Centre Singapore [56]	2013	100	20	90	55/0	74	50.9 (5 years)
Mount Sinai Medical Ctr, NY [57]	2014	170	29	37	52/4	40–79	30.6 (3 years)
Basingstoke/North Hampshire Hospital, UK [58]	2015	752	100	68	46/2	50	64.5 (5 years)
Wake Forest University, NC [59]	2015	430	100	44	28/3	n/a	53.4 (5 years)

[a]*CR* Cytoreduction
[b]*M/M* 30 Day morbidity and mortality
[c]*RR* Recurrence rate
[d]*SV* Survival
[e]Number calculated from graph by weighted average

peutic drugs are circulated throughout the abdominal cavity via pumps and heat exchangers (heart-lung machine). The most frequently used drug is mitomycin-c, which is administered for a duration of 60–120 min at a temperature of 41–43 °C. Other drugs have been used and are being tested without any increased benefit. Reconstructions and anastomoses are to be performed after the hyperthermic perfusion phase. Cytoreductive surgery and HIPEC are associated with formidable morbidity that may exceed 50% (Table 37-9). Apart from myelosuppression and nephrotoxicity with intensified diuresis, complications include sepsis, respiratory failure, ileus, anastomotic leak, abscess, enterocutaneous fistula, acute renal failure, thromboembolic events, and in the long run formation of hostile adhesions. The mortality rates in initial reports were approximately 10%, but could be reduced significantly in more recent series (Table 37-9). In the majority of reports, PCI score, PMCA tumor type and completeness of cytoreduction were significant prognostic factors. Perioperative or neo-adjuvant chemotherapy is currently a matter of debate and is not routinely used.

Conclusion

Appendiceal neoplasms are rare lesions. Most individual surgeons will encounter few, if any, during their career. Nevertheless, when a diagnosis of such a lesion is made, careful investigation of the histopathology and rational analysis of the various parameters are of paramount importance in order to finalize treatment and follow-up. There are numerous areas (e.g., incidentalomas, conservatively treated "appendicitis," perforated tumor without visible implants, and others) that await clarification of guidance which should be developed on preferably prospective data.

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